Primary CNS T-cell Lymphomas

A Clinical, Morphologic, Immunophenotypic, and Molecular Analysis

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Abstract: Primary central nervous system (CNS) lymphomas are relatively rare with the most common subtype being diffuse large B-cell lymphoma. Primary CNS T-cell lymphomas (PCNSTL) account for $<5\%$ of CNS lymphomas. We report the clinical, morphologic, immunophenotypic, and molecular characteristics of 18 PCNSTLs. Fifteen cases were classified as peripheral T-cell lymphoma, not otherwise specified, 2 of which were of γδ T-cell derivation and 1 was TCR silent; there was 1 anaplastic large cell lymphoma, ALK-positive and 2 anaplastic large cell lymphoma, ALK-negative. Median age was 58.5 years (range, 21 to 81 y), with an M:F ratio of 11:7. Imaging results showed that 15 patients had supratentorial lesions. Regardless of subtype, necrosis and perivascular cuffing of tumor cells were frequently observed (11/18 cases). CD3 was positive in all cases but 1; 10/17 were CD8-positive, and 5/17 were CD4-positive. Most cases studied had a cytotoxic phenotype with expression of TIA1 (13/15) and granzyme-B (9/13). Polymerase chain reaction analysis of T-cell receptor γ rearrangement confirmed a T-cell clone in 14 cases with adequate DNA quality. Next-generation sequencing showed somatic mutations in 36% of cases studied; 2 had >1 mutation, and none showed overlapping mutations. These included mutations in *DNMT3A*, *KRAS*, *JAK3*, *STAT3*, *STAT5B*, *GNB1*, and *TET2* genes, genes implicated previously in other T-cell neoplasms. The outcome was heterogenous; 2 patients are alive without disease, 4 are alive with disease, and 6 died of disease. In conclusion, PCNSTLs are histologically and genomically heterogenous with frequent phenotypic aberrancy and a cytotoxic phenotype in most cases.

Key Words: T-cell lymphoma, central nervous system, next-generation sequencing, γδ T cells, T-cell clonality, molecular diagnostics

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Primary central nervous system (CNS) lymphoma (PCNSL) is a relatively rare disease accounting for 2% to 6% of all primary brain malignancies and 1% to 2% of non-Hodgkin lymphoma.[1–5] These lymphomas are defined as being confined to the brain, spinal cord, or the eye without extra-CNS or lymph node manifestations at presentation.[1–6] However, late relapses outside the CNS can occur.[3,6] Although diffuse large B-cell lymphoma (DLBCL) is the most common type of PCNSL (with primary DLBCL of CNS enjoying a separate category in the current World Health Organization classification), other lymphomas including Burkitt lymphoma, mucosa-associated lymphoid tissue lymphomas (dura), follicular lymphoma, and T-cell lymphomas can present with intracranial disease.[2,3,7,8] The reported percentage of PCNSL of T-cell derivation

TABLE 1. Antibodies Used in the Immunophenotypic Analysis

Antigen	Clone	Dilution	Source
CD3	Polyclonal	1:100	Dako
CD4	1F6	1:40	Novocastra
CD8	C8/144B	1:50	Dako
CD2	AB75	1:160	Novocastra
CD5	4C7	1:100	Novocastra
CD7	CD7-272	1:50	Novocastra
βF1	8A3	1:20	Endogen
TCRγ	γ3.20	1:100	Thermo Scientific
CD30	1G12	1:50	Novocastra
ALK1	ALK1	1:400	Dako
TIA1	2G9A10FS	1:1000	Immunotech
Granzyme-B	GrB-7 + D170	1:100	Monosan
Perforin	KM585 PI-8	1:10	Vector
CD56	1B6	1:50	Novocastra
LMP1	CS1-4	1:400	Dako
Ki-67	MIB-1	1:50	Abcam

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TABLE 2. Clinical Features, Imaging, Treatment, and Outcome of PCNSTLs

Final No.	Age	Sex	Clinical Presentation	Imaging	Treatment	Outcome
1	21	M	Headache	Solitary, right occipital mass (2 cm)	Steroids, Thiotepa + HD MTX + XRT	NA
2	61	M	NA	Solitary frontal mass	NA	DOD
3	81	M	NA	Solitary, right occipital mass (2 cm)	Steroids	AwoD (64 mo)
4	54	M	Transient right facial and upper limb sensory symptoms, headaches, facial asymmetry, and speech difficulties	Solitary, left frontal mass	HD MTX + XRT	AwD (47 mo)
5	60	M	Headache	Solitary, left cerebellar mass (2.2 cm)	Chemotherapy	DOD (3 mo)
6	57	M	Difficulties short-term memory, ataxia, right leg weakness	Multiple lesions throughout the brain, largest left parietal lobe (3.5 cm)	NA	NA
7	69	M	NA	Solitary, right parietal mass	MTX + AraC + Leucovorin + Procarbazine hydrochloride	AwD
8	81	M	Altered mental status	Right occipital and temporal mass	2 × MTX + bendamustine	AwD (4 mo)
9	63	F	Left-sided weakness	Periventricular and striatocapsular abnormalities	No treatment	DOD
10	42	F	Seizures	Right frontal and temporal masses	Dexamethasone + HD AraC + 3 × MTX + 17 × XRT	AwD (5 mo)
11	21	F	Pregnant, headaches, behavior changes	Solitary parietal mass (7 × 7 × 5 cm)	NA	NA
12	67	F	Aphasia and facial paralysis	Multiple bilateral frontal and occipital masses	6 × HD MTX + XRT	AwoD (56 mo)
13	31	M	Seizure and slow (2 y) decline in mental function, weight loss, confusion	Bilateral temporal lobes enhancement	NA	NA
14	56	F	Headache	Solitary right frontal mass	NA	NA
15	57	M	Progressive neurological decline	Multiple lesions in the basal ganglia, midbrain, brachium pontis and cerebellar hemispheres	NA	DOD
16	43	M	Fever, nausea, vomiting (1 mo)	Multiple meningeal lesions (dural, leptomeningeal, spinal, superficial cortical parietal, right cerebellum, and medulla involvement)	NA	DOD
17	61	F	Weakness of right superior extremity, paresthesia, mild paralysis	Diffuse enhancement	Dexamethasone	DOD (1 mo)
18	62	F	History of multiple sclerosis, left lower extremity weakness (3 mo)	Solitary right frontal mass	NA	NA

AwD indicates alive with disease; AwoD, alive without disease; DOD, died of disease; HD, high dose; IT, intrathecal; MTX, methotrexate; NA, not available; XRT, radiation.

(PCNSTL) varies from 3.6% (France), 8.5% (Japan) to 2% (8 cases out of 370 patients) in the largest PCNSL series from the western world.[9] Choi et al[10] described a somewhat higher percentage of T-cell lymphomas (16.7%, 7/42 cases) in their series of PCNSL from Korea.

The most recently published large case series from the International Primary CNS Lymphoma Collaborative Group described 45 patients with PCNSTL.[1] In this series, 20 patients (44%) had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty-six patients (58%) had involvement of cerebral hemispheres, and 16 (36%) had lesions of deeper brain sites. The median disease-specific survival was 25 months, and multivariate analyses demonstrated an association of better ECOG performance status and methotrexate use with longer survival. However, a detailed morphologic and immunophenotypic analysis is not available. In a separate study of PCNSL other than DLBCL, outcomes for 7 patients with peripheral T-cell lymphomas (PTCL) were described; these T-cell lymphomas demonstrated similar or favorable clinical outcomes as

TABLE 3. Morphology, Immunophenotype, TCR Clonality, and Mutation Analysis

Case No.	Diagnosis	Size Cells	Necrosis	Perivascular Cuffing	Meningeal Spread	CD2	CD3	CD4	CD8	CD5
1	PTCL, NOS	Small-medium	Pos	Pos	Neg	NA	Pos	Pos	Neg	Pos
2	PTCL, NOS	Medium	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Pos F
3	PTCL, NOS	Small	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Pos
4	PTCL, NOS	Small-medium	Pos F	Pos	Neg	Pos F	Pos	Neg	Pos	Pos
5	PTCL, NOS	Medium	Pos	Neg	Neg	Pos	Pos	Mix	Mix	Pos F
6	PTCL, NOS	Large	Neg	Neg	Neg	Pos	Pos	Pos	Neg	Pos F
7	PTCL, NOS	Medium-large	Pos	Pos	Neg	Pos	Pos	Pos	Neg	Pos
8	PTCL, NOS	Medium-large	Pos	Pos	Neg	Pos	Pos	Pos	Neg	Pos
9	PTCL, NOS	Small-medium	Neg	Neg	Neg	Neg	Pos	Neg	Pos	Neg
10	PTCL, NOS	Small-medium	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Pos F
11	PTCL, NOS	Medium-large	Pos	Pos	Pos	Pos	Pos	Neg	Pos	Pos F
12	PTCL, NOS	Small	Pos	Pos	Pos	NA	Pos	Neg	Pos	Pos F
13	PTCL, NOS γδ	Small-medium	Neg	Pos	Neg	Pos F	Pos	Neg	Pos	Pos
14	PTCL, NOS γδ	Small-medium	Neg	Pos	Neg	NA	Pos	Neg	Pos	Neg
15	PTCL, NOS TCR silent	Medium	Neg	Neg	Neg	Pos	Pos	Neg	Pos	Neg
16	ALCL, ALK pos	Medium-large; "Hallmark" cells	Pos	Pos	Pos	Neg	Neg	Neg	Neg	Neg
17	ALCL, ALK neg	Large, "hallmark" cells	Neg	Neg	Neg	Pos	Pos	Neg	Pos W	Pos
18	ALCL, ALK neg	Large, "hallmark" cells	Pos	Neg	Neg	NA	Pos W	NA	NA	Neg

F indicates focal; GrB, granzyme-B; LMP1, EBV latent membrane protein; mix, mixed, both CD4-positive and CD8-positive cells present; mod, moderate; equiv, equivocal; NA, not available; neg, negative; no amp, no amplification products; not interp, not interpretable; pos, positive; rest, restricted; susp, suspicious; TRG, T-cell receptor gene rearrangement; US, unsatisfactory; w, weak; βF1, T-cell receptor βF1.

compared with previously reported data on DLBCLs.[7] Although several case series (referenced above) have made valuable contributions to the understanding of the clinical characteristics of PCNSTL, an extensive pathologic analysis/description is lacking. Several case reports and smaller case series have described the pathology and immunophenotype in varying detail.[11–26]

The goal of this study was to describe in a comprehensive manner not only the clinical characteristics but also the histologic, immunophenotypic, and molecular characteristics of 18 PCNSTLs identified from the consultation files of the hematopathology division of the authors' institution.

MATERIALS AND METHODS

Case Selection

Nineteen cases of PCNSTLs were identified from the pathology database of the Hematopathology Section, Laboratory of Pathology, National Cancer Institute, between 2000 and 2014. Eighteen cases were submitted in consultation as brain biopsies. One additional autopsy case was contributed by 1 of the coauthors (D.C.M.). None of the patients had lymphadenopathy or evidence of extra-CNS disease at the time of CNS presentation. One patient had a soft tissue mass involved by PTCL 3 months after diagnosis of the CNS lesion; given the close proximity of these lesions, this case was excluded. This study was approved by the Institutional Review Board of the National Cancer Institute.

Immunohistochemistry Studies

Immunohistochemical studies were performed on available formalin-fixed paraffin-embedded tissue (FFPE) sections using the following antibodies: CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD56, βF1, TCRγ, TIA1, granzyme-B, perforin, LMP1, MIB-1, and ALK1. The panel of antibodies, clone, dilution, and source are listed in Table 1. A case was scored as positive if > 50% of the atypical lymphoid cells expressed the antigen. MIB-1 was scored as low (< 33%), moderate (33% to 66%), and high (67% to 100%) on the basis of the percent of lymphoid cells positive.

TABLE 3. Morphology, Immunophenotype, TCR Clonality, and Mutation Analysis

Case No.	CD7	CD56	BF1	TCRγ	TIA1	GrB	Perf	CD30	ALK1	EBV	Ki-67	TRG PCR	Mutations
1	NA	Equiv	NA	NA	NA	NA	NA	NA	NA	Neg (LMP1)	NA	Pos	NA
2	Neg	Neg	Pos	NA	Pos	Pos	NA	Neg	NA	Neg (LMP1)	NA	Pos	NA
3	Pos F	Neg	Pos	NA	Pos	Neg	Neg	Neg	NA	Neg	Mod	Susp	*DNMT3A*, c.2207 G > T, p.Arg736Leu
4	Pos	Neg	Pos	NA	Pos	Neg	NA	Neg	Neg	Neg	High	Pos	WT
5	Pos F	Neg	Pos	NA	Pos	Neg	Neg	Neg	Neg	Rare	Mod	Rest	WT
6	Pos F	Not interp	Pos	NA	Neg	Neg	Neg	Neg	Neg	Neg	High	No amp	NA
7	Pos F	Neg	Pos	Neg	Pos	Pos	Pos F	Neg	Neg	Neg	Mod	Pos	WT
8	Pos F	Neg	NA	NA	NA	NA	NA	Neg	NA	Neg	Mod	Pos	NA
9	Pos	Neg	Pos	Neg	Pos	Pos	Pos	Neg	NA	NA	High	Pos	*KRAS*, c.34 G > A, p.Gly12Ser; *STAT5B*, c.1924 A > C, p.Asn642His; *JAK3*, c.1533 G > T, p.Met511Ile
10	Pos	Neg	Pos	Neg	Pos	Pos	Pos	Neg	Neg	Neg	High	Pos	WT
11	NA	NA	Pos	Neg	Pos	Pos	NA	Neg	Neg	Neg	NA	Pos	WT
12	NA	Neg	Neg	NA	Pos	NA	NA	NA	NA	Rare	High	Pos	NA
13	Pos	NA	Neg	Pos	Pos	Pos	NA	Neg	NA	Neg	Mod	Pos	WT
14	NA	NA	Neg	Pos	NA	NA	NA	NA	NA	NA	Mod	Pos	*TET2*, c.4034 A > C, p.Tyr1345Ser
15	Pos	Neg	Neg	Neg	Pos	Pos	NA	Neg	NA	Neg	High	Pos	*GNB1*,c.232 A > G, p.Lys78Glu; *STAT3*, c.1981G > C, p.Asp661His
16	Neg	Neg	US	NA	Pos	Pos	Pos	Pos	Pos C	Neg	High	Pos	WT
17	Pos F	Not interp	Pos	Neg	Pos F	Pos	NA	Pos	Neg	NA	Mod	No amp	NA
18	NA	Neg	NA	NA	Neg	NA	NA	Pos	Neg	Neg	High	Pos	NA

F indicates focal; GrB, granzyme-B; LMP1, EBV latent membrane protein; mix, mixed, both CD4-positive and CD8-positive cells present; mod, moderate; equiv, equivocal; NA, not available; neg, negative; no amp, no amplification products; not interp, not interpretable; pos, positive; rest, restricted; susp, suspicious; TRG, T-cell receptor gene rearrangement; US, unsatisfactory; w, weak; βF1, T-cell receptor βF1.

In Situ Hybridization for Epstein Barr Virus–encoded RNA

In situ hybridization was performed on FFPE tissue, using EBER1 DNP probe supplied by Ventana on an automated stainer (Ventana-Benchmark XT, Tucson, AZ). The ISH iView blue plus system with alkaline phosphatase and nitroblue tetrozolium and 5-bromo-4-chloro-3-indolyl phosphate substrate with Fast Red contrast was used for visualization, with relevant controls.

Molecular Studies

For *TRG* rearrangement, DNA was extracted from FFPE tissue blocks and either (1) single multiplexed polymerase chain reaction was carried out with primers directed against all known Vg family members, and the Jg1/2, JP1/2, and JP joining segments[27] or (2) 3 separate reactions were performed, 1 with primers Vg101, Vg11, and Jg12 (set 1), a second with primers Vg101, Vg11, and Jp12 (set 2), and a third with primers Vg9 and Jg12 (set 3), the first 2 performed according to the method of Slack et al[28] and the third according to a validated in-house method. Products were analyzed either by acrylamide gel electrophoresis or by capillary electrophoresis on an ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA). The results were interpreted as polyclonal, restricted, or clonal. The "restricted" *TRG*γ category was defined as an abnormal rearrangement pattern with small peaks that did not meet criteria for monoclonality, as previously described.[29]

Mutational Analysis

DNA samples were analyzed for somatic mutations within genes previously implicated in the pathogenesis of mature T-cell lymphomas using a targeted next-generation sequencing (NGS) strategy.[30] The mutation panel includes targeted regions of 38 genes previously reported to be mutated in T-cell lymphomas as well as targeted regions of genes involved in T-cell signaling focused on the JAK/STAT signaling pathway. The amplicon libraries were generated with 2 custom primer pools (total 227 amplicons) and were sequenced on an Ion Torrent Personal Genome Machine (PGM) (Life Technologies). The paraffin-embedded tissue sections were macrodissected to enrich for tumor cells with at least 20% tumor content. DNA was extracted using the Qiagen QIAamp DNA FFPE Tissue Kit and performed on a QIAcube according to the instructions of the manufacturer. Further details regarding the NGS methods (SDC1) and a list of the genes analyzed (SDC2) are included in Supplemental

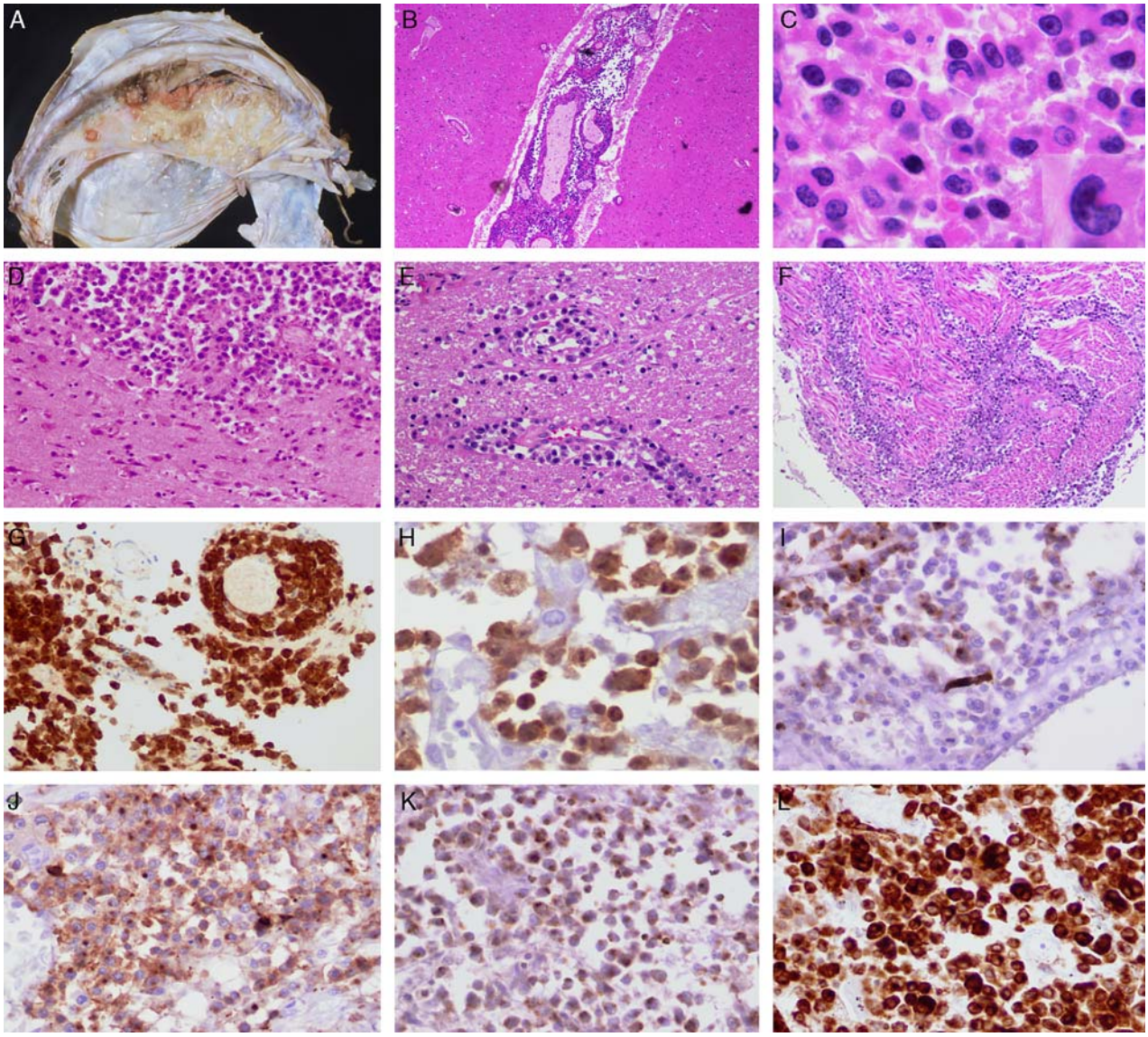

FIGURE 1. ALCL, ALK-positive (case 16). A, Multiple tan-white lesions are attached to the left side of falx dura. B, The leptomeninges are extensively involved. C, The cells are medium to large with irregular nuclei; occasional larger cells have eccentric kidney or horse shoe–shaped nuclei and abundant cytoplasm consistent with "hallmark cells." D, Parenchymal involvement was also seen along with perivascular infiltrates (E) as well as extensive spinal and nerve root involvement (F). The cells are positive for CD30 (G), ALK, nuclear, and cytoplasmic (H), focal EMA (I), CD43 (J), *TIA1* (K), and granzyme B (L).

Digital Content files (Supplemental Digital Content 1, http://links.lww.com/PAS/A305).

RESULTS

Clinical Features

Eighteen confirmed cases of PCNSTL were identified. The clinical features of these cases are summarized in Table 2. There were 11 men and 7 women, with a median age of 58.5 years (range, 21 to 81 y). The clinical manifestations of patients ranged from headache, aphasia, facial paralysis, facial and upper limb sensory abnormalities, speech abnormalities, ataxia, leg weakness, difficulties in short-term memory, etc. Imaging studies showed that 15 patients had supratentorial lesions, and 3 had cerebellar involvement. Solitary tumor was seen in 9 cases, multiple masses in 8, and 1 showed diffuse enhancement of meninges. None of the patients presented with or developed lymphadenopathy at any time point. One case of anaplastic large cell lymphoma (ALCL), ALK-positive diagnosed at autopsy (case 16), had extensive dural, leptomeningeal, and spinal disease. At autopsy one out of several lymph nodes tested showed rare scattered CD30-positive and ALK-positive cells, which were interpreted as secondary lymph node involvement by virtue of the high burden of the disease in the CNS and

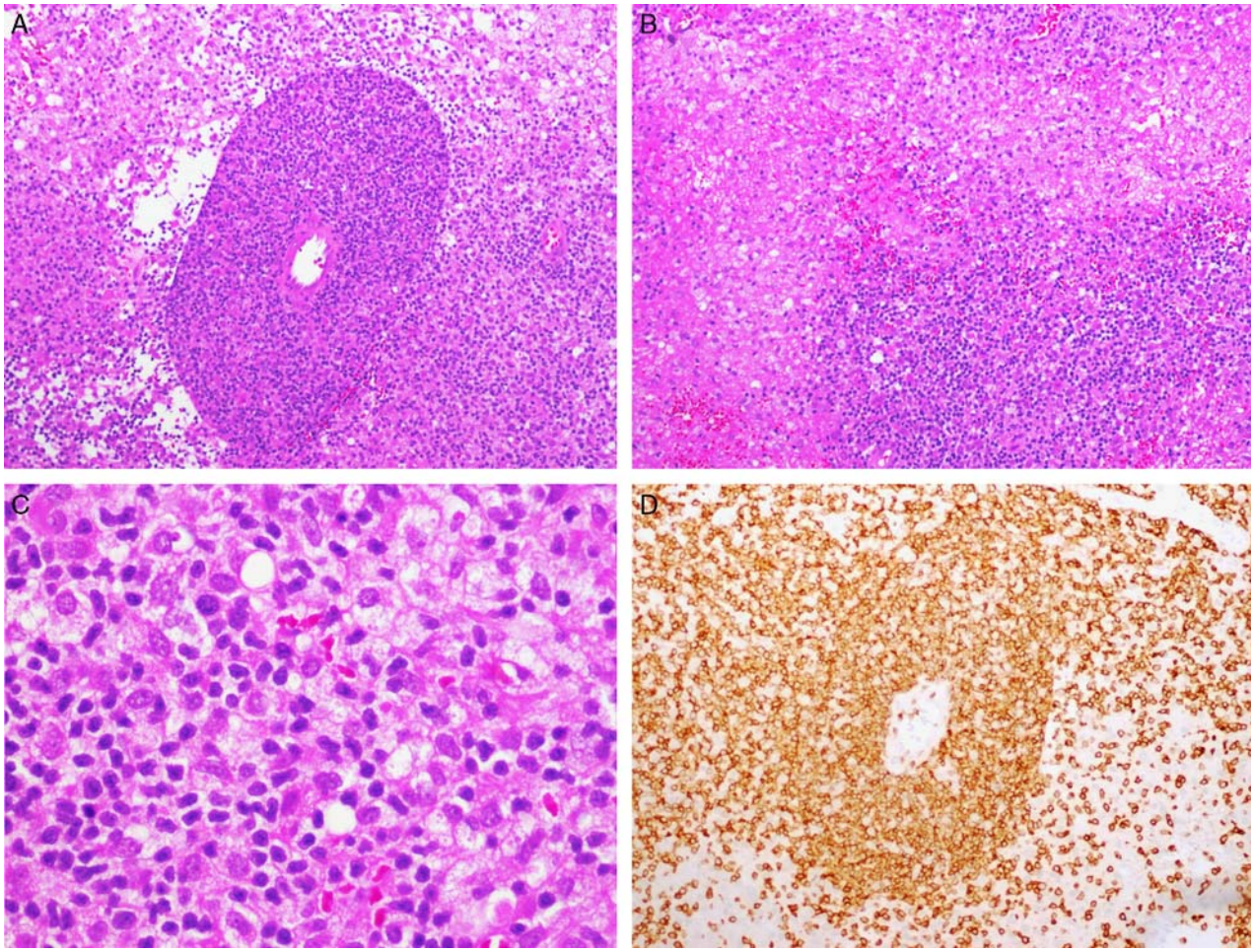

FIGURE 2. PTCL, NOS (case 1). A, Expansion of the Virchow-Robin space by an atypical lymphoid infiltrate. B, Broad areas of necrosis are visible. C, Neoplastic cells are small to medium in size with irregular nuclei; abundant admixed histiocytes are visible. D, The atypical cells are positive for CD3.

the lack of lymphadenopathy or histologically confirmed disease elsewhere.

Treatment information was available for 10 patients: 4 received chemotherapy and radiotherapy, 3 were treated with chemotherapy alone, 2 received only steroids, and 1 patient did not receive treatment due to a poor performance status. The outcome data were available for 12 patients. With a median follow-up of 5 months (range, 1 to 64 mo), 2 patients are alive without disease, 4 patients are alive with disease, and 6 patients died of disease.

Morphologic Findings

The PCNSTLs were classified as PTCL, not otherwise specified (NOS) (15 cases), ALCL, ALK-negative (2 cases), and ALCL, ALK-positive (1 case). The salient morphologic findings are summarized in Table 3. Although most cases were submitted as small biopsies, detailed gross examination was available for 1 ALCL, ALK-positive diagnosed at autopsy (case 16). This case demonstrated tan-white nodules on the dural surface (mostly left-sided) with size ranging from 0.3 to 0.8 cm (Fig. 1A). Leptomeningeal involvement was observed grossly in the lower thoracic and lumbar spinal cord with extension to the nerve roots of cauda equina. Overall, 5 cases had demonstrable leptomeningeal involvement.

Microscopically, most PTCL, NOS cases (11/15) were composed of atypical small and/or medium-sized lymphocytes with dense, hyperchromatic nuclei, irregular nuclear outlines, occasional distinct nucleoli, and scant cytoplasm (Fig. 2). Medium to large cells (3 cases) or mostly large cells (1 case) were predominant in the remainder (Fig. 3). Three cases showed features characteristic of ALCL, being composed of large cells with vesicular chromatin, evident nucleoli, and abundant cytoplasm; frequent "hallmark" cells were identified (Fig. 1C). The tumor cells formed cohesive aggregates/sheets in 2 cases and were scattered throughout the white matter in 1 case.

Prominent perivascular infiltration was evident in most cases (11/18) (Fig. 4), with tumor cells expanding the

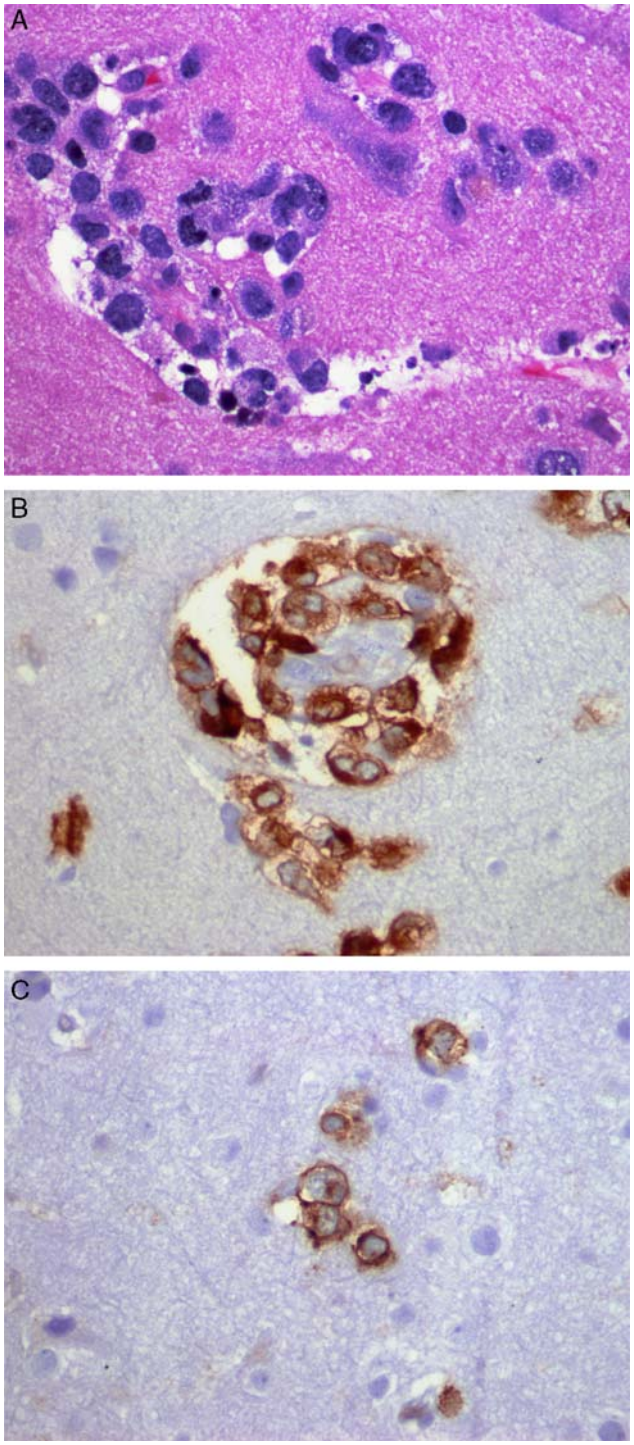

FIGURE 3. PTCL, NOS (case 6). A, A minority of cases, such as this one, contained large atypical cells with irregular nuclear contours, vesicular nuclei, and basophilic nucleoli. The neoplastic cells are CD3-positive (B) and CD4-positive (C).

Virchow-Robin space. Areas of necrosis were visible in 11 cases. Several cases demonstrated significant background gliosis and abundant histiocytes probably related to necrosis.

Immunophenotype

The atypical lymphoid cells expressed CD3 in all cases except 1 (ALCL, ALK-positive) (Table 3). Ten of 17 were CD8-positive, and 5/17 were CD4-positive, with no case showing dual expression. Partial or total loss of T-cell antigens was seen in 4/15 cases for CD2, 11/18 cases for CD5, and 8/13 cases for CD7. No case expressed CD56, although high background staining for CD56 (as expected in CNS tissues) made interpretation difficult. Ten of 14 cases showed βF1 immunostaining. Among the 4 βF1-negative cases, a γδ T-cell derivation was confirmed in 2 by positivity for TCRγ (Fig. 5), 1 case was TCR silent, and 1 lacked material for TCRγ. Regardless of histologic type, most of the cases showed a cytotoxic phenotype with expression of TIA1 in 13/15, granzyme-B in 9/13, and perforin in 4/7. Three (of 15) cases showed strong, uniform expression of CD30, corresponding to the diagnosis of ALCL, with one of these being positive for ALK, with both nuclear and cytoplasmic immunoreactivity. All 16 cases analyzed showed a brisk proliferation index as per Ki-67, with at least 50% of lymphoid cells positive. Rare Epstein Barr virus–positive cells were present in 2/15 cases studied by Epstein Barr virus–encoded RNA and/or LMP1. Stains for BCL6, CD10, and PD-1 (CD279) were performed on a single CD4-positive case (case 5) and were negative.

T-cell Receptor Gene Rearrangement and Mutational Analysis

The quality of DNA allowed for further analysis in 16/18 cases, with 2 cases showing no amplification products. A clonal rearrangement pattern was identified in 14 cases; 1 case showed a restricted pattern, and 1 was considered suspicious for a significant clonal rearrangement.

Eleven of 18 cases (1 of which was ALCL, ALK-positive) were analyzed with a custom NGS mutation panel targeting mutation hotspots in genes previously reported to be mutated in T-cell lymphomas and in genes involved in T-cell signaling pathways. Four cases of PTCL, NOS were found to have somatic mutations (4/11, 36%); 2 had >1 mutation, and none showed overlapping mutations. Case 3 displayed a *DNMT3A* (c.2207G > T; p.Arg736Leu) mutation. Case 9 was found to have *KRAS* (c.34G > A; p.Gly12Ser), *STAT5B* (c.1924A > C, p.Asn642His), and *JAK3* (c.1533G > T; p.Met511Ile) mutations. Case 14, PTCL, NOS of γδ T-cell derivation showed a *TET2* (c.4034A > C; p.Tyr1345Ser) mutation, and case 15, silent for TCR expression by immunostains, contained both *GNB1* (c.232A > G; p.Lys78Glu) and *STAT3* (c.1981G > C; p.Asp661His) mutations. All remaining cases were wild type at the targeted sites in the 38 genes included in the panel.

DISCUSSION

Through this study, we describe in detail the histopathologic, immunophenotypic, and molecular characteristics of 18 cases of PCNSTLs. Diagnosis of these

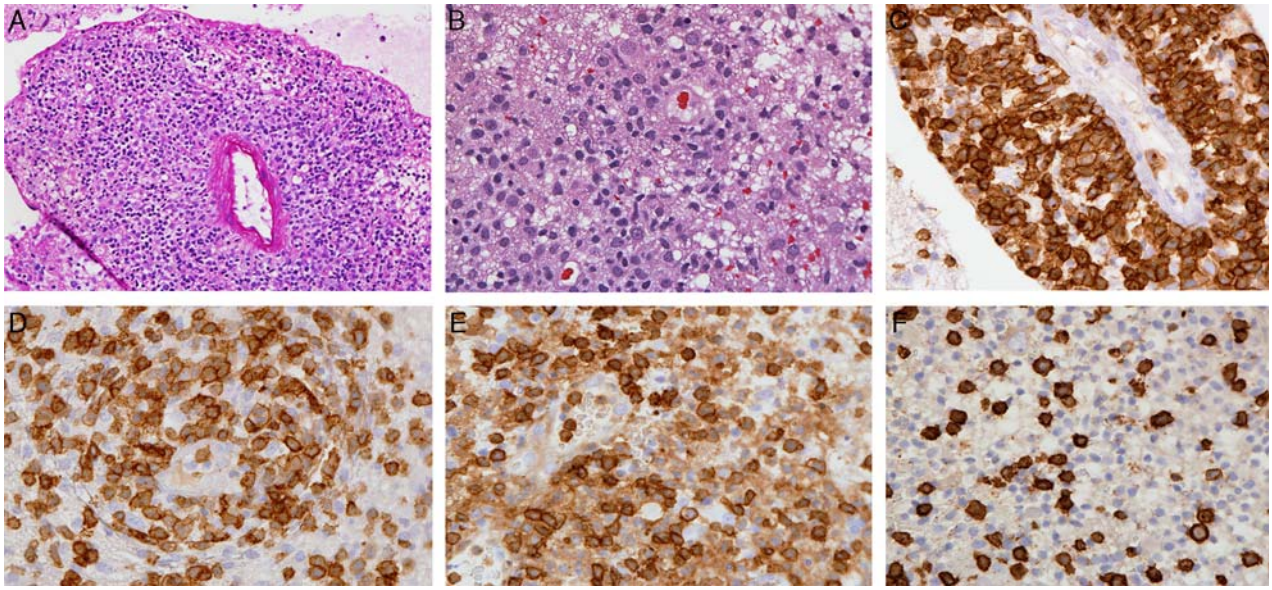

FIGURE 4. PTCL, NOS (case 8). A, Marked perivascular infiltration is present. B, The infiltrate is composed of small to medium atypical lymphocytes with significant background gliosis and abundant histiocytes. The atypical cells are strongly positive for CD2 (C), more variably positive for CD5 (D), positive for CD4 (E), and negative for CD8 (F).

lesions is often a challenge, with the main differential being an inflammatory process, as the neoplastic T cells were small to medium in size in the majority of cases, most of which were classified as PTCL, NOS. The diagnosis was more readily made in 3 cases of ALCL, 1 of which was positive for ALK. A helpful feature was prominent perivascular infiltration; perivascular cuffing is a common feature among both primary CNS B-cell and T-cell lymphomas. In addition, necrosis, gliosis, and histiocytic infiltration were seen in a significant number of cases. In contrast, abundant plasma cells, neutrophils, or eosinophils were absent; when present, these would favor an inflammatory process.

Given the small cell size in many cases, immunohistochemical studies and molecular analysis were key in diagnosis. The most common antigenic aberrancies included complete or partial loss of CD5 (61%) and CD7 (62%). Loss of CD3 was very uncommon, restricted to 1 case of ALCL. More than half were CD8-positive. Although most cases appeared to be derived from αβ T cells, 4 cases were βF1 negative, suggesting a γδ T-cell derivation. However, only 2 were positive for TCRγ by immunohistochemistry; 1 case was noted to be TCR silent, also a major aberrancy.[31] The majority of cases had a cytotoxic phenotype, irrespective of the histologic subtype, as determined by staining with granzyme-B, perforin, and TIA1. Prior studies have shown a high incidence of a cytotoxic phenotype in extranodal as opposed to nodal T-cell lymphomas.[32]

Molecular testing for *TRG* rearrangement played an important role in the diagnosis of PCNSTL. A clonal process was confirmed in 14/16 cases with adequate DNA, whereas 2 others were either suspicious or showed a restricted pattern. PCNSTLs have not been studied previously for molecular aberrations. Four of 11 PTCLs, NOS studied (36%) had mutations involving *STAT3*, *STAT5B*, *JAK3*, *DNMT3A*, *KRAS*, *TET2*, and *GNB1* genes. Interestingly, no mutation was common to multiple cases, suggesting molecular heterogeneity. However, the findings in 2 cases with mutations in *STAT5B*, *STAT3*, and *JAK3* support the importance of the JAK/STAT pathway in T-cell malignancies. Activating mutations of *STAT3*, *STAT5B*, and *JAK*s have been reported with high frequency in large granular lymphocytic leukemia,[33,34] γδ hepatosplenic T-cell lymphomas,[30] T-prolymphocytic leukemia,[35] nonhepatosplenic γδ T-cell lymphomas,[36] and natural killer/T-cell lymphoma.[37] Other studies have demonstrated the importance of the JAK/STAT pathway in both ALK-positive and ALK-negative ALCL.[38,39] Thus, our data suggest that JAK and/or STAT inhibitors might represent potential treatment options in patients with PCNSTLs.

DNMT3A and *TET2* mutations have been recently reported as important events in the pathobiology of mainly nodal lymphomas of T_{FH} derivation.[40,41] Interestingly, we found evidence of these mutations in PCNSTLs; 1 case with a mutation in *DNMT3A* had a CD4-positive phenotype, whereas a second case with a *TET2* mutation was of γδ T-cell derivation. *TET2* has not previously been implicated in the pathogenesis of γδ T-cell lymphomas.

Clinically, most of our cases of PCNSTL had supratentorial disease and at presentation had solitary masses. Most patients received some form of chemotherapy combined with steroids with or without intrathecal methotrexate and/or brain irradiation. Six patients had expired at the time of this study. In the largest series of PCNSTL of the western world (International Primary CNS Lymphoma Collabo-

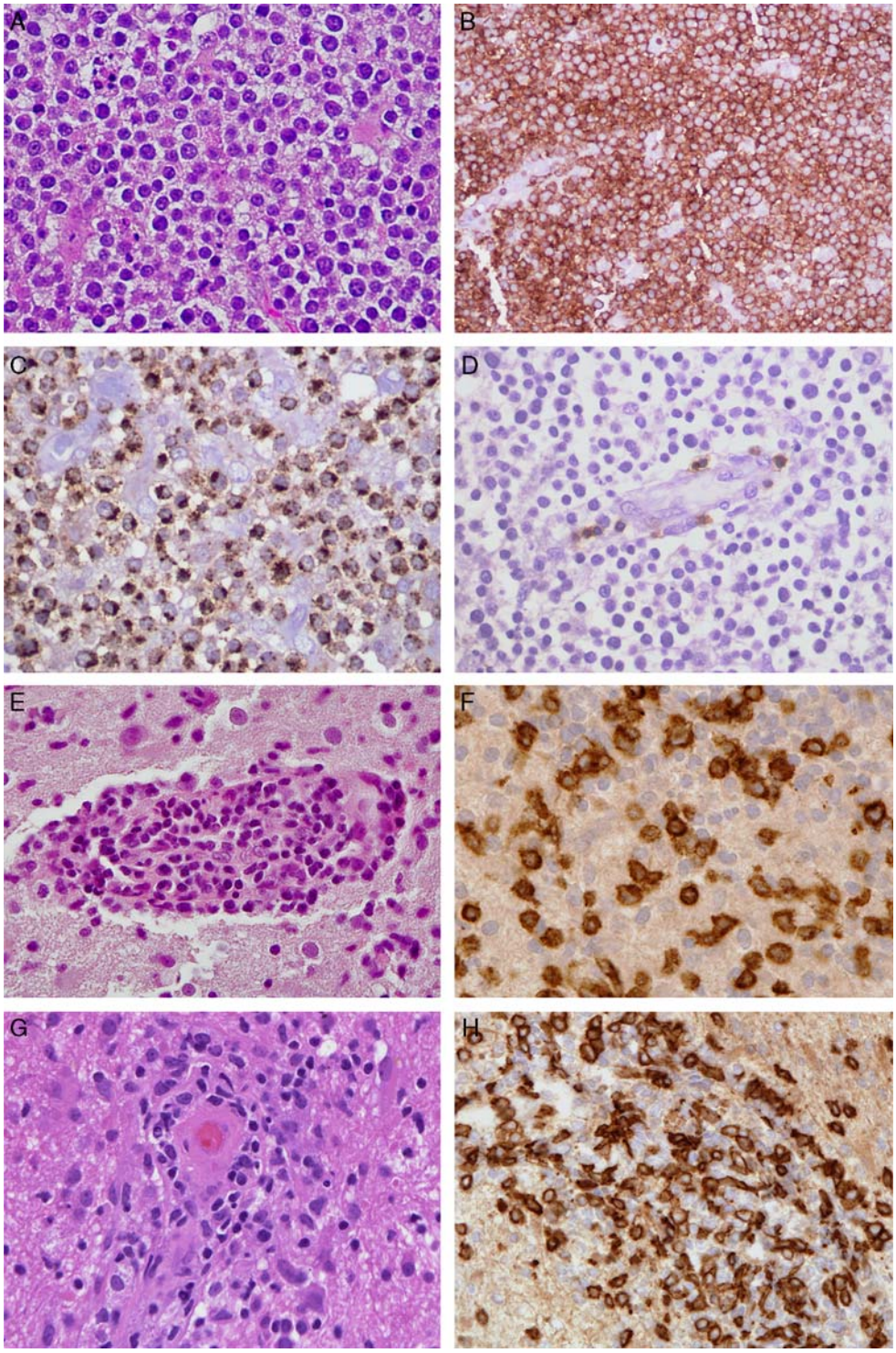

FIGURE 5. Phenotypic aberrancies in PCNSTL. A–D, PTCL, NOS with TCR silent phenotype (case 15). A, Monomorphic medium-sized atypical lymphocytes with irregular nuclear contours, vesicular chromatin, and occasional nucleoli. The neoplastic T cells are CD8-positive (B), TIA1-positive (C), and βF1-negative (D). TCRγ was also negative (not shown). E–H, TCRγ-positive cases (cases 13 and 14). The cells are mostly small to medium with irregular nuclear contours, admixed occasional larger cells, and demonstrate prominent perivascular cuffing (E and G). The cells are strongly positive for TCRγ immunostain (F and H).

rative Group),[1] the clinical characteristics were similar to those of PCNSLs in general[6,9,42] including the median age (approximately 60 y), propensity for supratentorial involvement, and male predominance. Similarly, PCNSLs of both B-cell and T-cell types are clinically aggressive, with median survivals of <2 years.[1,6,9,42]

Interestingly, a difference in prognosis based on morphology (ie, small, medium, vs. large cells) was not present for PCNSTL.[1] In a more recent study by Lim et al,[7] 9 patients with primary CNS PTCL were identified and demonstrated relatively favorable clinical outcomes as compared with primary CNS DLBCL. However, other than CD3 positivity in these cases, further histologic, immunophenotypic, and molecular data were not specified. Interestingly, a Korean study revealed a much higher percentage of PCNSTL cases (16.7%) of all PCNSLs,[10] significantly higher than that reported in western studies.

In a study by Levin et al,[16] 5 patients out of a cohort of 100 patients with PCNSL had T-cell lymphoma, and all of them presented with isolated leptomeningeal involvement. However, in the study describing the largest PCNSTL cohort, only 1 of 45 patients had leptomeningeal involvement.[1] In the other cases described in their study, the parenchyma of the cerebral hemispheres (cortex and white matter) were the most frequent site (64%) followed by deep brain structures. This is similar to the known manifestations of B-cell PCNSL.

In our study leptomeningeal involvement was present in 5 cases and was extensive in 1 (case 16, ALCL, ALK-positive). Involvement of the leptomeninges in ALCL is a common feature. Of the 24 cases of primary CNS ALCL that have been described,[21,25,43–61] 10 cases demonstrated some degree of dural or leptomeningeal involvement. In addition, there are 2 documented cases of primary dural ALCL without CNS parenchymal involvement.[44,45] In 1 case of ALCL from our series, the bulk of the disease was in the leptomeninges, and the clinical syndrome was dominated by meningitic signs and symptoms. Of the reported ALCL cases, 13 were ALK-positive, and 10 were ALK-negative, whereas data on 3 cases were unavailable. As expected, ALK positivity seems to correlate with a younger age and better prognosis (similar to that observed in systemic ALCL). Interestingly, leptomeningeal involvement does not seem to confer a worse prognosis.[40] Secondary involvement of the CNS is very rare in most PTCLs, being most often reported in ALCL in approximately 1% of cases.[62] The only PTCL that frequently involves the CNS is adult T-cell leukemia/lymphoma, which is a systemic disease in most patients.[63]

In conclusion, the diagnosis of T-cell lymphomas in the CNS is challenging, especially considering that the vast majority of these lymphomas have small or intermediate-sized cells with variable cytologic atypia. These need to be differentiated from reactive T-cell infiltrates and encephalitis caused by infections and autoimmune diseases. A combination of morphologic assessment, immunophenotypic aberrancies, and demonstration of clonal T-cell receptor rearrangement helps in establishing the diagnosis of a T-cell lymphoma. Preliminary genetic analysis identified mutations in genes involved in other mature T-cell malignancies but no common recurrent genetic events.

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